Diagnosing Angioedema

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KEYWORDS

• Angioedema • Hereditary angioedema • Diagnosis • Urticaria • Complement • Testing

KEY POINTS

- Angioedema is a symptom, defined as a localized and self-limiting edema of the subcutaneous and submucosal tissue, caused by a temporary increase in vascular permeability. Angioedema occurs most often within the setting of allergic diseases and of different forms of urticaria. In other cases, angioedema may be a disease.
- Location of the swelling, time to development, total duration, response to therapy, and family history help distinguish, among angioedema without urticaria, histamine- and non–histamine-dependent forms and hereditary from nonhereditary angioedema.
- Nonhistaminergic forms of angioedema include hereditary angioedema.
- Evaluation of recurrent angioedema should consider specific clinical signs and appropriate laboratory findings in establishing the correct diagnosis.

Angioedema is a symptom, defined as localized and self-limiting edema of the subcutaneous and submucosal tissue, caused by a temporary increase in vascular permeability. Most often it occurs within the setting of allergic diseases and of different forms of urticaria, but situations occur in which angioedema itself represents a disease. Quinke[1] was the first author who gave a separate description of these "circumscribed edema," which he called "angioneurotic edema." Shortly after Quinke, Osler,[2] in his seminal paper "Hereditary Angioneurotic Edema," gave the first exhaustive description of an angioedema as a separate nosologic entity.

Until the end of the 20th century, hereditary angioneurotic edema, renamed *hereditary angioedema* (HAE) by Rosen and Austen,[3] remained synonymous with hereditary deficiency of C1 inhibitor, the first biochemical defect identified to cause a recurrent form of angioedema.[4] In 2000, Bork and colleagues[5] described a series of families with a new form of HAE characterized by normal C1 inhibitor. From that point on, properly diagnosing a recurrent angioedema became a significant problem for the physician.

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In 2013, a physician who sees a patient for recurrent angioedema must consider specific clinical and laboratory signs to properly frame the patient and prepare a therapeutic plan.

CLINICAL DIAGNOSIS

The first clinical issue to be considered is presence or absence of concomitant wheals, which distinguishes urticaria from angioedema. Classification of urticaria was recently summarized, and angioedema occurring as part of the urticaria follows the same classification.[6,7] Location, time to development, total duration, and family history help to distinguish, among angioedema without urticaria, histamine- from non–histamine-dependent types and hereditary from nonhereditary angioedema (**Tables 1** and **2**). Recurrent abdominal pain due to temporary bowel occlusion caused by swelling within the gastrointestinal mucosa[8] is characteristic of HAE with and without C1 inhibitor deficiency, and of angioedema caused by acquired deficiency of C1 inhibitor. Oral and perioral location of angioedema is almost the rule in angioedema related to angiotensin-converting enzyme (ACE) inhibitors. Angioedema of the lips, or of half of them, is a frequent presentation for histaminergic forms, such as those prevented by H_1 antihistamine. These occurrences of angioedema are announced by local pruritic dysesthesia, peak rapidly within one or 2 hours, subside in 12 to 36 hours, and rarely affect the larynx.[7–9]

The relationship between angioedema and causative/facilitative factors is important to recognize. The presence of a clear chronologic cause-and-effect relationship is cardinal to diagnosing allergic angioedema, which, by definition, occur within a few hours, frequently minutes, of exposure to the offending agent. The same is true for most angioedema related to drugs, such as antibiotics or nonsteroidal anti-inflammatory drugs. More challenging is the identification of ACE inhibitors as a

Table 1
Clinical characteristics of different types of recurrent angioedema without wheals

	C1-INH HAE[a]	FXII HAE[b]	UNKN HAE[c]	Histam AE[d]	Non-Histam AE[e]	C1-INH AAE[f]	ACEi AE[g]
Peripheral angioedema	+++	+++	+++	+	+	++	+–
Tongue angioedema	+	+	+	++	++	++	+++
Laryngeal angioedema	+++	+++	+++	+	+	+++	+++
Gastrointestinal angioedema	+++	+++	+++	+–	+–	++	+–
Estrogen sensitivity	++	+++	+	–	–	–	–
Onset <6 h	+	+	+	+++	++	+	++
Duration >48 h	+++	+++	+++	+	+	+++	++
Family members with angioedema	+++	+	+++	–	–	–	–

[a] Hereditary angioedema with C1 inhibitor deficiency.
[b] Hereditary angioedema with a mutation in factor XII.
[c] Hereditary angioedema with an unknown defect.
[d] Recurrent, nonfamilial angioedema of undetermined origin (idiopathic) prevented by H_1 antihistamine treatment.
[e] Recurrent, nonfamilial angioedema of undetermined origin (idiopathic) not prevented by H_1 antihistamine treatment.
[f] Recurrent angioedema with nonfamilial (acquired) C1 inhibitor deficiency.
[g] Recurrent nonfamilial angioedema onset during treatment with angiotensin-converting enzyme inhibitors.

Table 2
Laboratory characteristics of different types of recurrent angioedema without wheals

Parameter	C1-INH HAE[a]	FXII HAE[b]	UNKN HAE[c]	Histam AE[d]	Non-Histam AE[e]	C1-INH AAE[f]	ACEi AE[g]
C1 inhibitor function <50% of normal	100%	0	0	0	0	100%	0
C1 inhibitor antigen <50% of normal	85%	0	0	0	0	85%	0
C4 antigen <12 mg/dL	>90%	Occasional	Occasional	Occasional	Occasional	>90%	Occasional
C1q antigen <50% of normal	Occasional	0	0	0	0	>70%	0
Mutation in SERPING1	>90%[h]	0	0	0	0	0	0
Mutation in FXII gene	0	100%	0	0	0	0	0

Percentage of patients carrying a specific parameter is derived from the literature reported in the text and from the authors' personal experience.
[a] Hereditary angioedema with C1 inhibitor deficiency.
[b] Hereditary angioedema with mutation in factor XII.
[c] Hereditary angioedema with unknown defect.
[d] Recurrent, nonfamilial angioedema of undetermined origin (idiopathic) prevented by H_1 antihistamine treatment.
[e] Recurrent, nonfamilial angioedema of undetermined origin (idiopathic) not prevented by H_1 antihistamine treatment.
[f] Recurrent angioedema with nonfamilial (acquired) C1 inhibitor deficiency.
[g] Recurrent nonfamilial angioedema onset during treatment with angiotensin-converting enzyme inhibitors.
[h] Genetic screening in patients with hereditary C1 inhibitor deficiency fails to identify a causative mutation in 3% to 8% of the patients, depending on the methodological approach.

cause of angioedema.[10] These drugs likely facilitate angioedema in patients who are slow bradykinin catabolizers.[11,12] In these patients, angioedema rarely occurs despite continued ACE inhibitor treatment, which frequently leads to delayed identification of the relationship between angioedema and the drug when this does occur. Therefore, a careful pharmacologic history should always be obtained for patients presenting with angioedema. The fact that a treatment was started years before onset of symptoms does not rule out a potential relationship; this is always true for ACE inhibitors, and should also be considered in patients taking estrogens, which is another treatment that may affect angioedema. In addition to relatively rare instances in which estrogens directly cause angioedema, this treatment frequently worsens angioedema with and without C1 inhibitor deficiency.[13,14] Identifying the close relationship between the occurrence of angioedema and elevated estrogen levels from pregnancy or estrogen-containing pills can be nearly diagnostic for HAE with mutations in factor XII.[15]

Accurate recording of family history may be the only tool for diagnosing HAE, because HAE is not limited to the hereditary deficiency of C1 inhibitor or the presence of mutations in factor XII, but can be inherited in the absence of an identified genetic or biochemical marker.[16] This familial HAE seems to be still transmitted as an autosomal dominant trait, the same identified by Crowder and Crowder in 1917[17] for the form subsequently related to mutations in the C1 inhibitor gene.[18,19] HAE with normal C1 inhibitor and no mutations in factor XII is estimated to represent approximately 70% of the hereditary forms that are not related to C1 inhibitor deficiency. Hence, diagnosis of HAE with normal C1 inhibitor and absence of factor XII mutations is purely dependent on clinical evidence of a family history of angioedema. Determining the presence of angioedema within the family is not always straightforward, particularly when dealing with abdominal symptoms and cutaneous manifestations ranging between angioedema and urticaria. Approximately half of the general population will experience at least a single urticarial eruption. Therefore, physicians should carefully distinguish sporadic manifestations from a true family history of recurrent angioedema. Distribution of symptoms according to an autosomal mode of inheritance reinforce the finding, but the number of family members available for evaluation may be a limiting factor preventing conclusive diagnosis.

Clinical penetrance of a genetic abnormality is another factor that may affect family history. The 2 forms of angioedema that have been related to a specific genetic defect significantly differ in this respect, with C1 inhibitor deficiency having a penetrance approaching 100%, and factor XII mutations remaining clinically silent in men, and sometimes also not expressed in female carriers.[20] In families in which inheritance has not yet been related to a specific marker, penetrance obviously cannot be evaluated.

LABORATORY DIAGNOSIS

The measurement of C1 inhibitor is the core laboratory test for angioedema diagnosis. Deficiency of C1 inhibitor is the abnormality that best accounts for the presence of recurrent angioedema. It is mandatory to screen for C1 inhibitor deficiency all patients with angioedema without wheals whose symptoms do not subside during antihistamine treatment, including those who become symptomatic during ACE inhibitor or estrogen treatment. It is not uncommon for these drugs to induce the clinical expression of an underlying C1 inhibitor deficiency that has remained silent.[21,22] However, screening for C1 inhibitor deficiency is not univocally defined. Direct identification of all deficient patients requires the determination of C1 inhibitor function, because

hereditary and acquired deficiency of this protein may be characterized by the presence of protein products detected by quantitative methods but devoid of functional activity. Dysfunctional C1 inhibitor is detected in approximately 15% of both hereditary and acquired C1 inhibitor deficiency (Marco Cicardi, personal case list). Two methods are currently available to measure C1 inhibitor function, and neither is routinely performed in diagnostic laboratories.[23] Both methods are based on measurement of the capacity of plasma to inhibit the esterase activity of a fixed amount of C1 esterase, quantified by chromogenic or immunoenzymatic assay. The chromogenic assay has higher specificity than the immunoenzymatic assay, whose normal values must be established by each laboratory to properly diagnose C1 inhibitor deficiency.

Measurement of C1 inhibitor and C4 antigen, routinely performed in most laboratories, can partially overcome the problem of diagnosing C1 inhibitor deficiency when the functional assay is not available. C1 inhibitor antigen fewer than 50% of normal diagnoses 85% of the deficiencies. The value of C4 measurement is indicated by the fact that C1 inhibitor deficiency causes hyperactivation of the classical complement pathway and C4 consumption. Thus, very few patients with C1 inhibitor deficiency (<10% in the authors' case list) have C4 plasma levels greater than 12 mg/dL. The high variability of the levels of this protein in the normal population, and the several diseases that may lead to C4 consumption (eg, systemic lupus erythematosus, cryoglobulinemia), reduce the specificity of this measurement. Nevertheless, levels of C4 greater than 12 mg/dL make the diagnosis of C1 inhibitor deficiency very unlikely.

When the diagnosis of C1 inhibitor deficiency has been established, measurement of the plasma levels of C1q may help distinguish between hereditary and acquired deficiency: this subcomponent of the C1 complex is almost always normal in HAE and very low in 70% of the acquired deficiencies.[24] Changes in several proteins of the contact, coagulation, and fibrinolytic systems have been identified during angioedema symptoms in patients with C1 inhibitor deficiency.[25–28] However, none of these parameters has yet achieved diagnostic value.

Genetic testing is the sole laboratory approach for diagnosing factor XII HAE. Three mutations—2 different missense mutations of codon p.Thr328 and the deletion of 72 base pairs located in the same factor XII gene region—have been shown to segregate with family symptoms of angioedema.[29] One of these mutations (Arg328Lys) accounts for most of the factor XII-HAE families described to date.[30–32] Sequencing of the short region of factor XII containing all mutations causing HAE is therefore enough for the genetic diagnosis of this type of angioedema. The controversial evidence of the effect of these mutations on factor XII activity prevents biochemical assays from being helpful in diagnosis.[33,34]

Genetic testing is less compelling for diagnosing HAE and C1 inhibitor deficiency; diagnosis usually occurs when combining biochemical findings and family history. Genetic testing is limited to situations in which a single member of the family has angioedema symptoms and C1 inhibitor deficiency, and distinction between acquired and genetic deficiency is not clear-cut. In these circumstances, the genetic basis of the disease can only be demonstrated with the evidence that the C1 inhibitor gene (SERPING1) carries a mutation preventing circulation of a normal protein in plasma. Most C1 inhibitor HAE families have so-called private mutations (ie, each family has its own mutation), and more than 300 different mutations have been associated to genetic C1 inhibitor deficiency.[35–38] Genetic diagnosis of C1 inhibitor deficiency is therefore complicated and is achieved through sequencing a preidentified mutated region in SERPING1 or all exons and exon/intron boundaries.

No biochemical or genetic marker can identify other types of angioedema. Tryptase, as marker of mast cell degranulation, could help identifying histamine-mediated angioedema, but it is not used in clinical practice because of the high number of false-negative results. Very limited help comes from allergy testing, which confirms diagnosis only when a causative agent was previously identified.

In conclusion, distinguishing between angioedema and urticaria is important for determining an appropriate therapeutic approach. Careful evaluation of the clinical clues, along with proper C1 inhibitor and genetic testing, provide the major insights for correct diagnosis.

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